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Original Article

Modifying surgical extents in patients with preoperatively presumed early-stage endometrial cancer based on ProMisE classification: a retrospective, single-center study

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ABSTRACT

Objective: This study aimed to explore differences in disease extent based on the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) classification and to establish personalized staging surgery strategies in patients with preoperatively presumed uterus-confined endometrial cancer.
Methods: In this retrospective, single-center study, we reviewed the medical records of patients with endometrial cancer. These patients were classified according to the ProMisE classification based on tissue samples obtained from dilation and curettage or staging surgeries, and the disease extent was analyzed based on pathologic reports.
Results: A total of 345 patients were clinically estimated to be in stage 1/2 before staging surgery, with immunohistochemistry (IHC) results available. This cohort included 332 patients (96.2%) with clinical stage 1 and 13 patients (3.8%) with stage 2 based on the 2009 FIGO staging system. Among these, 81 patients (23.5%) were assigned to an mismatch repair deficient group (MMRd), 33 (9.6%) to an abnormal p53 group, and 123 (71.1%) to a no specific molecular profile (NSMP) group. Overall, 13 patients had nodal metastasis, with a higher rate observed in the abnormal p53 group (1.2%, 12.1%, and 2.2% for the MMRd, abnormal p53, and NSMP groups, respectively, p=0.013). One patient (0.3%) had parametrial metastasis and four (1.1%) had peritoneal metastasis.
Conclusion: Patients with abnormal p53 IHC results exhibited a higher likelihood of lymph node metastasis, even when initially presumed to be at an early stage. For the abnormal p53 group, proactive lymphadenectomy surgery appears beneficial for accurate staging and establishing a subsequent treatment plan.

Keywords: Endometrial Neoplasms; Molecular Typing; Molecular Diagnostic Techniques; Neoplasm Staging; Lymphatic Metastasis

Synopsis

This study investigated the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) classification in uterus-confined endometrial cancer. Abnormal p53 was associated with increased nodal metastasis, suggesting benefits of lymphadenectomy. ProMisE enables tailored surgical strategies based on molecular profiles and disease extent.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Data Availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions
Conceptualization: L.J.Y.; Data curation: P.E.; Investigation: P.E.; Methodology: K.S.W., K.Y.T.; Project administration: L.J.Y.; Supervision: L.J.Y.; Validation: N.E.J., K.S.; Writing - original draft: L.J.H.; Writing - review & editing: L.J.H.

INTRODUCTION

Endometrial cancer is the sixth most common cancer among women in the United States, with an estimated 417,000 new cases and 97,000 fatalities reported in 2020. The incidence rate is the highest in Northern America, at 21.1 cases per 100,000 individuals, compared with the 8.2 cases per 100,000 in Eastern Asia. This disparity suggests the significant role of lifestyle factors associated with westernization in the development of this disease [1,2].

Various classification methods, including diagnostic procedures, surgical staging, and postoperative adjuvant therapy, have been developed to determine the most appropriate treatment options for endometrial cancer. In 1983, Bokhman [3] introduced a classification system based on pathogenic characteristics of the disease, classifying endometrial cancer into two types: type 1 and type 2. High-risk histologies, such as uterine papillary serous carcinoma, clear cell carcinoma, carcinosarcomas (malignant mixed Müllerian tumors), and undifferentiated/dedifferentiated carcinomas, typically require aggressive treatment rather than fertility-sparing options according to guidelines [4-7]. The Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) classification uses immunohistochemistry (IHC) for mismatch repair (MMR) proteins and tumor protein 53 and sequencing for polymerase-ε exonuclease domain mutations (POLE EDMs) to categorize endometrial cancer into the following four groups: POLE EDM group, MMR deficiency (MMRd) group, abnormal p53 group, and no specific molecular profile (NSMP) group [8]. The ProMisE classification demonstrated differences in progression-free survival and overall survival among these groups using Kaplan-Meier curves. In addition, the European Society for Medical Oncology clinical practice guidelines for endometrial cancer combined the ProMisE classification with stage, histological type, grade, lymphovascular space invasion (LVSI) status, and myometrial invasion to organize patients into a three-tier risk grouping. This system proposed different adjuvant therapeutic strategies for each risk groups [9]. Additionally, the RAINBO trial is exploring the possibility of treatment differences among these groups [10-12].

However, these classification systems do not explain which treatments should be administered to which groups and why. Despite being a key component in the management of endometrial cancer, surgical treatment strategies remain undifferentiated. The necessity of hysterectomy for endometrial cancer treatment is indisputable. However, the importance of lymphadenectomy in patients without myometrial invasion lacks sufficient evidence. In this study, we hypothesized that ProMisE classified groups may differ in terms of the initial diagnostic stage or disease extent. This study aimed to investigate whether there is a significant difference in disease extent among groups classified by ProMisE in patients with clinical stage II or lower cancer confined to the uterus. If a relationship is identified, it can inform decisions regarding the scope of surgical intervention.

MATERIALS AND METHODS

In this retrospective, single-center study, we analyzed the electronic medical records of patients with histologically confirmed endometrial cancer who had undergone staging surgeries. Among these, we included patients who had no extrauterine disease on pelvic magnetic resonance imaging or positron emission tomography-computed tomography but who underwent lymph node dissection during the staging surgeries. From this group, we selected patients who had results for p53 IHC, MSH6 IHC, and PMS2 IHC from either

dilatation and curettage (D&C) or surgical specimens. Given that no patients with POLE EDMs are available for testing, patients with loss of PMS2 or MSH6 on IHC were initially classified into the MMRd group. The remaining patients were assigned to the abnormal p53 group if they had abnormal p53 results or to the NSMP group. We analyzed the association between these three groups and the disease extent based on the surgical pathology reports.

We recorded patients' age at diagnosis, body mass index (BMI), and preoperative CA125 levels. Additionally, we assessed medical comorbidities, specifically noting whether the patients were receiving medications for hypertension, diabetes mellitus (DM), or thyroid disease. Patients were staged preoperatively and postoperatively using the 2009 and 2023 FIGO staging systems for endometrial cancer.

We categorized the histological types of the tumors as endometrioid carcinoma, serous carcinoma, clear cell carcinoma, carcinosarcoma, mucinous carcinoma, mixed carcinoma, adenosquamous carcinoma, and mesonephric carcinoma. Based on the final pathological report, we verified the presence of LVSI and metastasis to the cervix, uterine serosa, adnexa, vagina, parametrium, peritoneum, pelvic lymph nodes, and para-aortic lymph nodes. We also documented the use of brachytherapy, external beam radiotherapy, and chemotherapy as adjuvant postoperative treatments.

As of July 15, 2024, we recorded the last follow-up date and determined whether the patients had experienced recurrence or death by that time.

This study was reviewed and approved by the Institutional Review Board of Severance Hospital and performed in accordance with the International Conference on Harmonization-Good Clinical Practice standards.

Continuous variables are expressed as means and standard deviations. The mean differences across the groups for age at diagnosis, BMI, initial CA125 levels, and medical comorbidities were analyzed using the Kruskal–Wallis test and Welch's ANOVA test. Group proportions for stage, medical comorbidities, mode of operation, histologic types, adjuvant therapy, recurrence, death, and disease extent were analyzed using Fisher's exact and Cochran–Armitage tests. Statistical analyses were performed using R Studio software (Version 4.3.3) on a computer with an Intel Core i7 processor running Windows 10 Home.

RESULTS

A total of 581 patients were newly diagnosed with endometrial cancer and underwent staging surgery between January 14, 2020, and February 28, 2024. We excluded 57 patients with clinical stage III disease and 43 patients with clinical stage IV disease. Of the remaining 481 patients, 136 without IHC results were excluded, leaving 345 patients for analysis. Among these, 81 patients (23.5%) were included in the MMRd group, 33 (9.6%) in the abnormal p53 group, and 231 (67.0%) in the NSMP group.

Regarding baseline characteristics, the age at diagnosis was higher in the abnormal p53 group than in the other groups (mean ± standard deviation, 55.8±7.5, 62.7±9.4, 53.0±11.83 years in the MMRd, abnormal p53, and NSMP groups, respectively; $p<0.001$). No significant

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Table 1. Baseline characteristics of patients (n=345)

Variables	Total (n=345)	MMR deficiency group (n=81)	Abnormal P53 group (n=33)	NSMP group (n=231)	p-value
Age at diagnosis (yr)	54.6±11.1	55.8±7.5	62.7±9.4	53.0±11.8	<0.001
BMI at diagnosis (kg/m^2)	25.5±5.0	24.4±3.6	24.2±3.7	26.1±5.4	0.067
Initial CA125	30.5±59.6	25.8±25.3	33.0±72.3	31.8±65.9	0.640
Medical comorbidity					
None	203 (58.8)	54 (66.7)	14 (42.4)	135 (25.8)	
Hypertension	96 (27.8)	20 (24.7)	15 (45.5)	67 (29.0)	0.10
Diabetes mellitus	44 (12.8)	5 (6.17)	4 (12.1)	30 (13.0)	0.250
Thyroid disease	36 (10.4)	4 (5.0)	5 (15.2)	19 (8.23)	0.190

Data are expressed as mean ± standard deviation or number (%).
BMI, body mass index; MMR, mismatch repair; NSMP, no specific molecular profile.

differences were observed among the groups in terms of BMI at diagnosis; initial CA125 levels; or prevalence of hypertension, DM, and thyroid disease (**Table 1**).

The patients underwent one of three types of surgery: laparoscopy, robot-assisted laparoscopy, or open surgery. Laparoscopy was performed in 170 patients (49.3%), robot-assisted laparoscopy in 135 (39.1%), and laparotomy in 40 (11.6%), with no significant differences in the mode of surgeries among the three groups (p=0.300). All patients underwent pelvic or para-aortic lymph node dissection; 217 patients (62.9%) underwent sentinel lymph node mapping, whereas 128 patients (37.1%) underwent conventional lymph node dissection. This distribution was similar across the three groups (p=0.716).

Based on the 2009 FIGO staging system for preoperative clinical staging, the cancer in 332 patients (96.2%) was classified as stage I and 13 (3.77%) as stage II. The abnormal p53 group had a significantly higher proportion of stage II cases (6.2%, 12.1%, and 1.7% for the MMRd, abnormal p53, and NSMP groups, respectively; p=0.004). Regarding postoperative final staging, the cancer in 21 patients (6.0%) was upstaged to stage III or IV: 6 patients (7.4%) in the MMRd group, 4 (12.1%) in the abnormal p53 group, and 11 (4.7%) in the NSMP group, with no significant difference among the groups (p=0.110) (**Table 2**).

Based on the 2023 FIGO staging system for preoperative clinical staging, the cancer in 289 patients (83.8%) was classified as stage I and 52 (15.1%) as stage II. The abnormal p53 group had a significantly higher proportion of stage II cases (19.8%, 45.5%, and 9.1% for the MMRd, abnormal p53, and NSMP groups, respectively; p<0.001). Regarding postoperative final staging, the cancer in 21 patients (6.0%) was upstaged to stage III or IV: 6 patients (7.4%) in the MMRd group, 4 (12.1%) in the abnormal p53 group, and 11 (4.7%) in the NSMP group, with significant differences among the groups (p<0.001) (**Table 2**).

The distribution of histological types among the three groups showed no significant differences (p=0.716). The proportion of patients with endometrioid carcinoma was 76 (93.8%) in the MMRd group, 19 (57.6%) in the abnormal p53 group, and 217 (93.9%) in the NSMP group. Among patients with endometrioid carcinoma, the abnormal p53 group had a significantly lower proportion of grade 1 tumors (32.9%, 21.1%, and 49.3% for the MMRd, abnormal p53, and NSMP groups, respectively; p=0.005). Additionally, the proportion of aggressive histological types, excluding grade 1 or 2 endometrioid carcinoma, was significantly higher in the abnormal p53 group (24.7%, 57.6%, and 15.6% for the MMRd, abnormal p53, and NSMP groups, respectively; p<0.001) (**Table 3**).

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Table 2. Shift in stage between the three groups

Variables	Total (n=345)	MMR deficiency group (n=81)	Abnormal P53 group (n=33)	NSMP group (n=231)	p-value
Preoperative 2009					0.004
1	332 (96.2)	76 (93.8)	29 (87.9)	227 (98.3)	
2	13 (3.8)	5 (6.2)	4 (12.1)	4 (1.7)	
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Postoperative 2009					0.110
1	306 (88.7)	73 (90.1)	25 (75.8)	208 (90.0)	
2	18 (5.2)	2 (2.5)	4 (12.1)	12 (5.2)	
3	20 (5.8)	6 (7.4)	4 (12.1)	10 (4.3)	
4	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	
Upstaged	37 (10.7)	7 (8.6)	7 (21.2)	23 (10.0)	0.074
Downstaged	6 (1.7)	3 (3.7)	1 (3.0)	2 (0.9)	
Preoperative 2023					<0.001
1	289 (83.8)	65 (80.2)	18 (54.5)	206 (89.2)	
2	52 (15.1)	16 (19.8)	15 (45.5)	21 (9.1)	
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
NA	4 (1.16)	0 (0.0)	0 (0.0)	4 (1.7)	
Postoperative 2023					<0.001
1	251 (72.8)	56 (69.1)	11 (33.3)	184 (79.7)	
2	73 (21.2)	19 (23.5)	18 (54.5)	36 (15.6)	
3	20 (5.8)	6 (7.4)	4 (12.1)	10 (4.3)	
4	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	
Upstaged	63 (18.3)	16 (19.8)	11 (33.3)	36 (15.6)	0.067
Downstaged	12 (3.5)	5 (6.2)	1 (3.03)	6 (4.3)	
NA	4 (1.2)	0 (0.0)	0 (0.0)	4 (1.7)	

Data are expressed as number (%).
Four patients could not be evaluated for preoperative 2023 staging because the histologic type could not be determined from the preoperative tissue, making the staging shift unknown.
MMR, mismatch repair; NA, not applicable; NSMP, no specific molecular profile.

Table 3. Pathological characteristics of the three groups

Variables	Total (n=345)	MMR deficiency group (n=81)	Abnormal P53 group (n=33)	NSMP group (n=231)	p-value
Histology					0.720
Endometrioid	312 (90.4)	76 (93.8)	19 (57.6)	217 (93.9)	0.009
Grade 1*	136 (43.6)	25 (32.9)	4 (21.1)	107 (49.3)	
Grade 2*	133 (42.6)	36 (49.4)	10 (52.6)	87 (40.1)	
Grade 3*	43 (13.7)	15 (19.7)	5 (26.3)	23 (10.6)	
Serous	12 (3.5)	1 (1.2)	10 (30.3)	1 (0.4)	
Mixed	6 (1.7)	4 (4.9)	0 (0.0)	2 (0.9)	
Carcinosarcoma	6 (1.7)	0 (0.0)	2 (6.06)	4 (1.7)	
Clear cell	6 (1.7)	0 (0.0)	2 (6.06)	4 (1.7)	
Mucinous	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	
Adenosquamous	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	
Mesonephric	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	
Aggressive histological types	75 (21.7)	20 (24.7)	19 (57.6)	36 (15.6)	<0.001
Immunohistochemistry					
MMR deficient	0 (0.0)	81† (100.0)	0 (0.0)	0 (0.0)	
MSH6 loss	20 (5.8)	20 (24.7)	0 (0.0)	0 (0.0)	
PMS2 loss	65 (18.8)	65 (80.2)	0 (0.0)	0 (0.0)	
Abnormal p53	42 (12.2)	9 (11.1)	33 (100.0)	0 (0.0)	
Overexpression	33 (9.6)	9 (11.1)	24 (72.7)	0 (0.0)	
Absence	5 (1.5)	0 (0.0)	5 (15.2)	0 (0.0)	
Cytoplasmic	4 (1.2)	0 (0.0)	4 (12.1)	0 (0.0)	

Data are expressed as number (%).
MMR, mismatch repair; NSMP, no specific molecular profile.
*The proportion of endometrioid carcinoma within each group when considered a whole is as follows.
†Four patients exhibit concurrent loss of MSH6 and PMS2.

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We also examined metastasis to various organs among the three groups. Cervical involvement was noted in 20 patients (5.8%), with 3 in the MMRd group, 5 in the abnormal P53 group, and 12 in the NSMP group. Uterine serosal involvement was present in one patient from the NSMP group. Seven patients (2.0%) had adnexal involvement, including 2 from the MMRd group, 1 from the abnormal P53 group, and 4 from the NSMP group. There were no cases of vaginal involvement. Parametrial invasion was observed in one patient, classified under the NSMP group. Peritoneal metastasis was found in 4 patients (1.2%), with 1 in the MMRd group, 1 in the abnormal P53 group, and 2 in the NSMP group. In the study, lymph node metastasis was identified in 13 patients (3.8%), with distribution among the groups as follows: 4 in the MMRd group, 4 in the abnormal P53 group, and 5 in the NSMP group. Of these, 8 patients had metastasis confined to the pelvic lymph nodes, while 5 had metastasis extending to the paraaortic lymph nodes. While no significant associations were found between the groups and other organ metastases, the abnormal p53 group had a higher rate of lymph node metastasis (4.9%, 12.1%, and 2.2% for the MMRd, abnormal p53, and NSMP groups, respectively; p=0.017), with a significantly higher risk of pelvic lymph node metastasis (1.2%, 12.1%, and 2.2% for the MMRd, abnormal p53, and NSMP groups, respectively; p=0.013) (**Table 4**, **Fig. 1**).

DISCUSSION

The study demonstrated that the abnormal p53 group had a higher proportion of patients diagnosed at stage II at initial diagnosis. Even when expected to be at stage II or lower, this group had more cases of pelvic lymph node metastasis than the other groups. Additionally, this group had a higher proportion of aggressive histological types and a lower proportion of grade 1 tumors among cases of endometrioid carcinoma.

The abnormal p53 group showed a higher proportion of patients with cervical metastasis, although this was not statistically significant, suggesting a possible association with cervical metastasis (3.7%, 15.2%, and 5.2% for the MMRd, abnormal p53, and NSMP groups, respectively; p=0.059) (**Table 4**). Given the confirmed association between lymph

Table 4. Disease extent in the three groups

Variables	Total (n=345)	MMR deficiency group (n=81)	Abnormal P53 group (n=33)	NSMP group (n=231)	p-value
LVSI	63 (18.3)	16 (19.8)	9 (27.3)	38 (16.5)	0.190
Cervix	20 (5.80)	3 (3.7)	5 (15.2)	12 (5.2)	0.059
Uterine serosa	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	1.000
Adnexa	7 (2.0)	2 (2.5)	1 (3.03)	4 (1.7)	0.570
Lymph node	13 (3.8)	4 (4.9)	4 (12.1)	5 (2.2)	0.017
L1	10 (2.9)	1 (1.2)	4 (12.1)	5 (2.2)	0.013
L2	5 (1.5)	3 (3.7)	0 (0.0)	2 (0.9)	0.160
Conventional		2 (2.5)	1 (3.0)	1 (0.4)	
Sentinel		1 (1.2)	1 (3.0)	4 (1.7)	0.640
Conventional L1	6 (1.7)	0 (0.0)	3 (9.1)	3 (1.3)	
Conventional L2	5 (1.4)	2 (2.5)	0 (0.0)	3 (1.3)	
Sentinel L1	5 (1.4)	1 (1.2)	1 (3.0)	3 (1.3)	
Sentinel L2	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.9)	
Vagina	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Parametrium	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	1.000
Peritoneum	4 (1.1)	1 (1.2)	1 (3.0)	2 (0.9)	0.370

Data are expressed as number (%).
LVSI, lymphovascular space invasion; MMR, mismatch repair; NSMP, no specific molecular profile.

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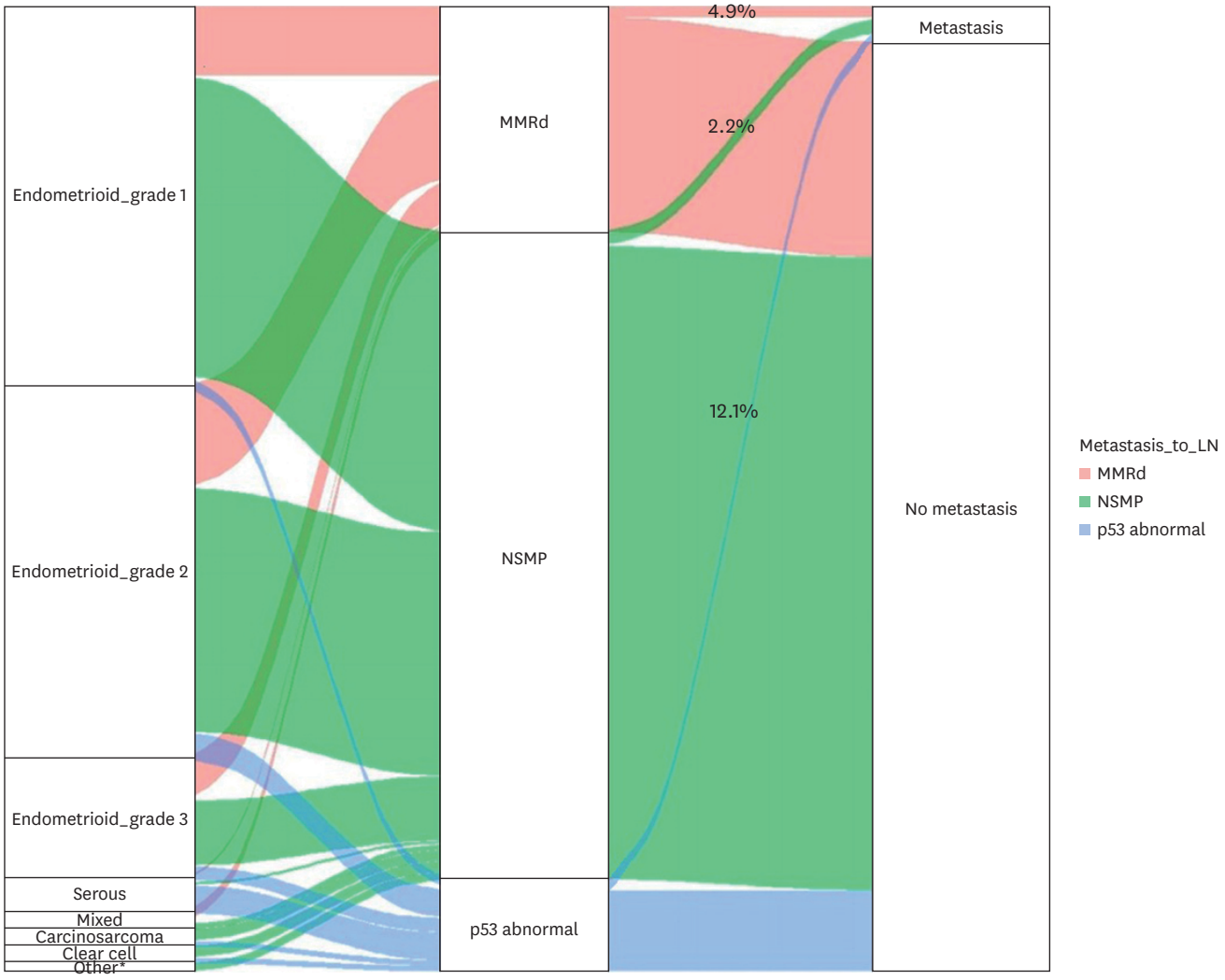

Fig. 1. Alluvial plot illustrating the relationships among histologic type, the Proactive Molecular Risk Classifier for Endometrial Cancer classification, and lymph node metastasis.
MMRd, mismatch repair deficient; NSMP, no specific molecular profile.
*The "other" category includes one case each of mucinous, adenosquamous, and mesonephric types, all of which are part of the NSMP group.

node metastasis and abnormal p53 expression, which is indicative of stage III disease, it is anticipated that with a larger sample size, an association with stage II disease involving cervical lesions may also be confirmed.

Previous studies on abnormal p53 expression and disease extent included patients at all stages. A systematic review involving 912 patients found that 90% of endometrioid carcinoma cases in the abnormal p53 group were grade 3, and the lymph node metastasis rate was significantly higher (23.7%) than that in the other groups [13]. Another study reported that among 74 patients, the abnormal p53 group, which included 18 patients (24.3%), was associated with lymph node metastasis ($p<0.001$). This trend was confirmed even though the participants in our study were early-stage patients [14].

Real-world data from all patients with endometrial cancer who underwent staging operations during a specific period at a tertiary medical center, excluding certain cases that did not meet

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the criteria, accurately reflected the characteristics of the entire patient population and the prevalence of each group.

And during surgery, all patients underwent intraperitoneal exploration by experienced gynecologic oncologists and all received lymph node dissection. Out of the total 345 patients, 305 underwent minimally invasive surgery enabled by Firefly mode, with 217 of these patients performing sentinel lymph node mapping to visually confirm lymphatics and accurately conduct dissections.

One major limitation is the absence of POLE sequencing, which prevents identification of the POLE mutation group, the second group classified under the ProMisE classification. So, the MMRd group in our study represents a pure MMRd group. However, individuals with POLE mutations might have been included in the remaining groups. Particularly, dual mutations of POLE and p53 could have resulted in some POLE mutation cases being classified within the abnormal p53 group, as concurrent abnormal p53 expression was noted. Literature suggests that among 319 individuals, 30 had a POLE mutation (9.4%), and 16 exhibited more than one molecular feature, with 3 out of 4 individuals with a POLE mutation also showing a p53 mutation [8]. This supports the likelihood of POLE mutation cases being subsumed under the abnormal p53 category in our analysis (**Fig. 2**).

Despite the inclusion of the small, prognostically favorable POLE mutation cohort, the abnormal P53 group in this study exhibited a significantly more extensive disease burden compared to other groups. These findings highlight the marked impact of abnormal p53 gene on disease progression.

The inability to include the entire ProMisE classification makes it difficult to generalize the study's findings. In the Republic of Korea, the cost for IHC testing to assess MMR gene mutations and p53 status was about $120, while NGS testing to determine POLE gene status

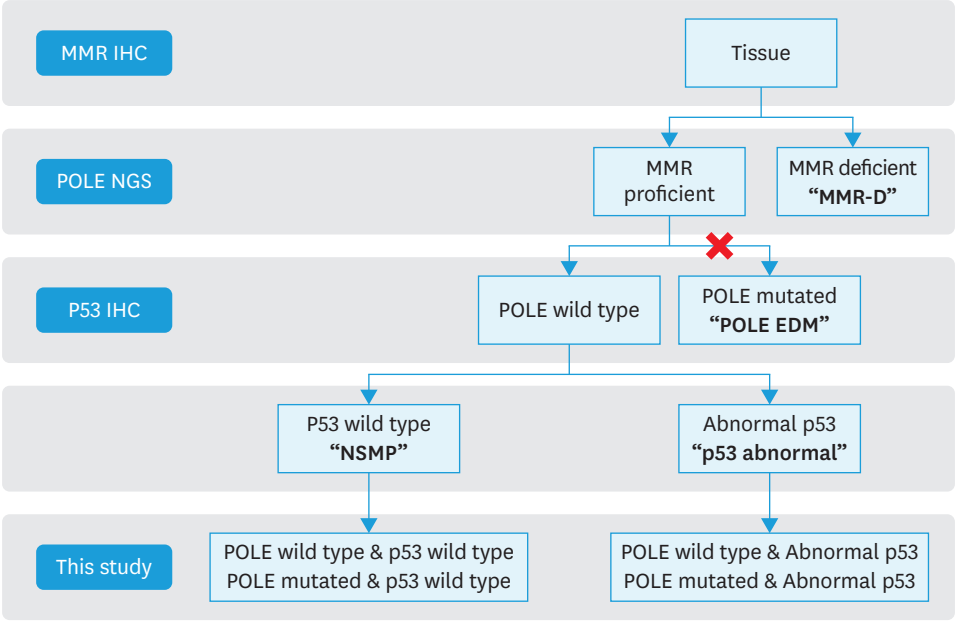

Fig. 2. Steps in molecular classification with ProMisE in this study.
MMRd, mismatch repair deficient; NSMP, no specific molecular profile.

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was about $1100 as of the dates between January 14, 2020, and February 28, 2024. The cost of testing for the POLE gene exceeds that of a laparoscopic staging operation, highlighting the real-world challenges to ideal classification.

The abnormal p53 group was likely to be at a more advanced stage than that indicated by the preoperative clinical assessment. Therefore, in clinical practice, it is crucial to avoid delays in treatment and to perform aggressive lymph node assessments if abnormal p53 expression is detected in D&C specimens, even if myometrial invasion is not expected. However, the efficacy of lymphadenectomy in the absence of myometrial invasion remains unclear.

The MRC ASTEC trial, which included 1,408 patients with clinical stage I endometrial cancer, compared patients who underwent lymphadenectomy with those who did not and found no benefit in overall or recurrence-free survival. The hazard ratio (HR) for overall survival was 1.04 (0.74–1.45; p=0.830) and that for recurrence-free survival was 1.25 (0.93–1.66; p=0.140) [15]. Conversely, the SEPAL study compared 325 patients who underwent pelvic lymph node dissection with those who underwent para-aortic lymph node dissection. For patients with an intermediate or high risk of recurrence, combined pelvic and para-aortic lymphadenectomy reduced the risk of death compared with pelvic lymphadenectomy alone (HR=0.44; 0.30–0.64; p<0.001) [16].

First, this study confirmed the trends in metastatic patterns among the groups; however, further research on the pathophysiology underlying these trends is necessary. Although the initial disease extent showed that the abnormal p53 group had higher lymph node metastasis rates, long-term follow-up is required to determine whether this could serve as a predictive factor for specific treatment outcomes.

Additionally, the 2023 FIGO staging system has upstaged aggressive histological types and myometrial invasion, along with abnormal p53 with myometrial invasion, to stage 2. We found a significantly higher proportion of aggressive histological types in the group with abnormal p53 expression (**Table 4**). Future research should explore the relationship between these two factors, including their chronological or inclusion relationships and their relative risk effects.

The study indicates that preoperative D&C specimens can be used for the ProMisE classification. If a patient is identified as part of the abnormal p53 group, there is an expected likelihood of postoperative upstaging. This allows for identification of patients who could benefit from aggressive lymphadenectomy.

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